Exhibit A

Systemic Lupus Erythematosus

(Disseminated Lupus Erythematosus)

The Merck Manual of Diagnosis and Therapy

Section 5. Musculoskeletal And Connective Tissue Disorders

Chapter 50. Diffuse Connective Tissue Disease

Topics

Rheumatoid Arthritis
Sjögren's Syndrome
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Relapsing Polychondritis
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navigation help

A chronic inflammatory connective tissue disorder of unknown cause that can involve joints, kidneys, serous surfaces, and vessel walls and that occurs predominantly in young women but also in children.

Of SLE cases, 90% occur in women. Increased awareness of mild forms of SLE has resulted in a worldwide rise in reported cases. In some countries, the prevalence of SLE rivals that of RA. The sera of most patients contain antinuclear antibodies (ANA), often including anti-DNA antibodies. The pathogenesis of autoimmune reactions is discussed in Ch. 148.

Pathology, Symptoms, and Signs

Clinical findings vary greatly. SLE may begin abruptly with fever, simulating acute infection, or may develop insidiously over months or years with episodes of fever and malaise. Vascular headaches, epilepsy, or psychoses may be initial findings. Manifestation: referable to any organ system may appear. **Articular symptoms,** ranging from intermittent arthralgias to acute polyarthritis, occur in approximately 90% of patients and may exist for years before other manifestations appear. In long-standing disease, capsular insertional erosions at the metacarpophalangeal joints with marked secondary joint deformity may occur without x-ray evidence of obvious marginal erosions (Jaccoud's arthritis). However, most lupus polyarthritis is nondestructive and nondeforming.

Cutaneous lesions include characteristic malar butterfly erythema (see Plate 50-1); discoid lesions (see Discoid Lupus Erythematosus, below); and erythematous, firm, maculopapular lesions of the face, exposed areas of the neck, upper chest, and elbows. Blistering and ulceration are rare, although recurrent ulcers on mucous membranes (particularly the centra portion of the hard palate near the junction of the hard and soft palate, the buccal and gum mucosa, and the anterior nasal septum) are common. Generalized or focal alopecia is

common during active phases of SLE. Mottled erythema on the sides of the palms with extension onto the fingers, periungual erythema with edema, and macular reddish purple lesions on the volar surfaces of the fingers also may occur. Purpura may develop secondary to thrombocytopenia or necrotizing angiitis of small vessels. Photosensitivity occurs in 40% of patients.

Recurrent pleurisy, with or without effusion, is common. Lupus pneumonitis is rare, although minor pulmonary function abnormalities are common. Life-threatening pulmonary hemorrhage may rarely occur. **Pericarditis** is often present. More serious rare complications are **coronary artery vasculitis** or **fibrosing myocarditis. Libman-Sacks lesions** are described under Noninfective Endocarditis in Ch. 208.

Generalized adenopathy is common, particularly in children, young adults, and blacks. **Splenomegaly** occurs in 10% of patients. Histologically, the spleen may show periarterial fibrosis (onion skin lesion).

CNS involvement can cause headaches, personality changes, stroke, epilepsy, psychoses, and organic brain syndrome. Cerebral or pulmonary artery thrombosis or embolism, although rare, is associated with anticardiolipin antibodies (see Laboratory Findings, below).

Renal involvement may be benign and asymptomatic or relentlessly progressive and fatal. The most common manifestation is proteinuria. The histopathology of the renal lesion varies from a focal, usually benign glomerulitis to a diffuse membranoproliferative glomerulonephritis. Because milder cases of lupus have been increasingly detected, the percentage of patients with clinically significant renal disease has declined.

Acute lupus hemophagocytic syndrome is a rare presentation of SLE, with fever and fulminant pancytopenia, described in Asians (particularly of Chinese descent), among whom SLE has a high incidence. Bone marrow shows proliferation of reactive histiocytes, with phagocytosis of hemopoietic cells (an example of the reactive hemophagocytic syndrome). There is no evidence of underlying infection. Patients respond promptly to corticosteroids.

Laboratory Findings

The fluorescent test for ANA screens for SLE; positive ANA tests (usually in high titer) occur in > 98% of SLE patients and should lead to more specific tests for anti-double-stranded DNA antibodies (an enzyme-linked immunosorbent assay or the slightly less sensitive but more specific crithidia slide method). High titers of anti-double-stranded DNA antibodies, if present, are highly specific for SLE.

Other ANA and anticytoplasmic antibodies (eg, Ro [SSA], La [SSB], Sm, RNP, Jo-1) are diagnostically valuable in SLE or in other connective tissue diseases (as described below). Because Ro is predominantly cytoplasmic, anti-Ro antibodies may occasionally be found in ANA-negative SLE patients presenting with chronic cutaneous lupus. Anti-Ro is the causal antibody for neonatal lupus and congenital heart block. Anti-Sm is highly specific for SLE but, as with anti-double-stranded DNA, is not sensitive.

False-positive serologic tests for syphilis occur in 5 to 10% of SLE patients. They may be associated with a positive test for the **lupus anticoagulant** or a prolonged partial thromboplastin time. Abnormal values in one or more of these assays indicate the presence of antiphospholipid antibodies (eg, anticardiolipin antibodies), which are associated with arterial or venous thrombosis, spontaneous abortion, late fetal loss, and thrombocytopenia. Anticardiolipin antibodies may be directly assessed by enzyme-linked immunosorbent assay.

Serum complement levels are often depressed in active disease and are usually lowest in patients with active nephritis. ESR is elevated almost uniformly during active disease. C-reactive protein levels may be strikingly low in SLE, even with ESR > 100 mm/h. Leukopenia is the rule, notably lymphopenia in active SLE. Hemolytic anemia may occur. Autoimmune thrombocytopenia may be severe and life threatening. The presentation of SLE is occasionally indistinguishable from idiopathic thrombocytopenic purpura.

Renal damage can become evident at any time, even when other features of SLE are absent A high or rising level of anti-DNA antibody may predict an increased risk of lupus nephritis. Renal biopsy is usually not necessary for diagnosis but may help evaluate the status of renal disease (ie, active inflammation vs. postinflammatory scarring) and guide medical therapy. Urinalysis may be repeatedly normal despite early renal involvement confirmed by biopsy; thus, it should be performed at regular intervals while monitoring patients in apparent remission. RBC and granular casts suggest more active nephritis.

Diagnosis

SLE is obvious when a patient (particularly a young woman) is febrile with an erythematou skin rash, polyarthritis, evidence of renal disease, intermittent pleuritic pain, leukopenia, and hyperglobulinemia with anti-double-stranded DNA antibodies. Early-stage SLE can be difficult to differentiate from other connective tissue disorders and may be mistaken for RA if arthritic symptoms predominate. Mixed connective tissue disease has the clinical features of SLE with overlapping features of systemic sclerosis, rheumatoid-like polyarthritis, and polymyositis or dermatomyositis (see below).

Meticulous evaluation and long-term observation may be required before SLE is diagnosed Patients with discoid lesions must be evaluated to differentiate discoid lupus erythematosus from SLE. Some drugs (eg, hydralazine, procainamide, β-blockers) produce positive ANA tests and, occasionally, a lupuslike syndrome associated with antihistone antibodies. These features usually disappear if the drug is withdrawn promptly. The American College of Rheumatology has proposed criteria for the classification (not for diagnosis) of SLE (see Table 50-3).

Prognosis

The more severe the disease, the greater the risk of iatrogenic drug-induced complications, which further increase morbidity and mortality. Examples include infection from immunosuppression and coronary artery disease from chronic corticosteroid use. In genera the course of SLE is chronic and relapsing, often with long periods (years) of remission. During the past two decades, the prognosis has improved markedly. Provided the initial

acute phase is controlled, the long-term prognosis is usually good. Flares are rare after menopause, although late-onset SLE does occur and may be difficult to diagnose. The 10-y survival in most developed countries is > 95%. This very improved prognosis underlines th paramount importance of early diagnosis of SLE. Sometimes, however, the presentation may be acute and disastrous (eg, with cerebral thrombosis or late fetal loss).

Treatment

Management of idiopathic SLE depends on its manifestations and severity. To simplify therapy, SLE should be classified as mild (fever, arthritis, pleurisy, pericarditis, headache, or rash) or severe (life-threatening disease, eg, hemolytic anemia, thrombocytopenic purpura, massive pleural and pericardial involvement, significant renal damage, acute vasculitis of the extremities or GI tract, florid CNS involvement). The course is unpredictable.

Mild or remittent disease may require little or no therapy. Arthralgias are usually controlled with NSAIDs. Aspirin is useful, especially in patients with the thrombotic tendency associated with anticardiolipin antibodies, but high doses in SLE may cause liver toxicity. Antimalarials help, particularly when joint and skin manifestations are prominent. Regimens vary, but hydroxychloroquine 200 mg po once or twice per day is preferred. An alternative is chloroquine 250 mg/day po or quinacrine (mepacrine) 50 to 100 mg/day po. Combinations of these drugs are sometimes used. Ophthalmologic examination usually is advised at 6-mo intervals, although this practice may be excessively cautious because these doses are modest and recent data suggest that hydroxychloroquine has very low retinal toxicity. DHEA 50 to 200 mg/day may decrease the need for other drugs, especially corticosteroids. Larger doses are less well-tolerated for their androgenic effect and are probably not more effective than the lower dose range.

Severe disease requires immediate corticosteroid therapy. A combination of prednisone an immunosuppressive drugs is recommended in active, serious CNS lupus or active reversibl lupus nephritis. Starting oral prednisone dosages for specific manifestations are as follows: hemolytic anemia, 60 mg/day; thrombocytopenic purpura, 40 to 60 mg/day (platelet count may not rise for 4 to 6 wk); severe polyserositis, 20 to 60 mg/day (response begins within days); renal damage, 40 to 60 mg/day in combination with immunosuppressive drugs. Improvement does not usually occur for 4 to 12 wk and may not be evident until corticosteroid dosage is reduced. Azathioprine in doses up to 2.5 mg/kg/day or cyclophosphamide 2.5 mg/kg/day is often used as an immunosuppressive drug for renal SLE. There is a strong trend toward intermittent or cyclical "pulsing" with immunosuppressive drugs, such as cyclophosphamide approximately 500 mg IV (together with mesna and fluid loading to protect the bladder), repeated monthly for >= 6 to 12 mo depending on the renal response and hematologic tolerance (see Table 50-4).

Acute vasculitis and severe CNS lupus are treated with the same regimens as for renal damage, above. In situ thrombosis or embolism of cerebral, pulmonary, or placental vessel: may require short-term treatment with heparin and longer term management with warfarin. In CNS lupus or other critical crises, methylprednisolone 1000 mg by slow (1-h) IV infusion on 3 successive days often is the initial form of treatment, together with IV cyclophosphamide, as above.

Suppressive therapy: Mild or severe chronic disease should be treated with the minima dose of corticosteroids and other drugs that will control tissue inflammation (eg, antimalarials, low-dose immunosuppressants). Corticosteroid dosage is usually determined by decreasing it 10% at intervals (depending on the rate of clinical improvement). For example, if fever and arthritis are the initial active manifestations, the dose is reduced at weekly intervals; if thrombocytopenia and renal disease (both of which respond more slowly to initiation of therapy) are problems, the dose is reduced q 2 to 4 wk. Rebound (temporary flare) and relapse tend to occur in the system with the most recent exacerbation Response to therapy is measured by relief of symptoms and signs or improvement in laboratory tests. Anti-double-stranded DNA antibody titers or low serum complement level may return to normal with treatment. Clinical rather than serologic features are all-important in determining therapy. With daily prednisone < 15 mg, a gradual change to alternate-day dosing may be possible. Most SLE patients can be weaned off prednisone. Th need for long-term high-dose corticosteroids often leads to consideration of alternative oral immunosuppressive drugs for their steroid-sparing effects.

General medical management: Intercurrent infection, often complicating the disease and easily mistaken for some of its manifestations, should be treated vigorously. The usual measures to combat heart failure and renal insufficiency must be taken, in addition to using suppressive drugs. ACE inhibitors may be useful for both congestive heart failure and proteinuria. Close medical supervision is imperative during surgical procedures and pregnancy, but if cardiac and renal functions are adequate, pregnancy is not contraindicated in relatively inactive SLE. However, spontaneous abortion and postpartum disease flares ar frequent. The latter usually are easily controlled, given increased vigilance in the puerperium. Hypersensitivity rashes are common with sulfonamides, trimethoprim-sulfamethoxazole, and penicillin. Flares and vascular thrombosis may occur with oral contraceptives but are rare. Long-term anticoagulation is vital in patients with antiphospholipid antibodies and recurrent thrombosis (see Ch. 131). Patients with antiphospholipid antibodies may experience early or late fetal loss caused by placental vessel thrombosis and ischemia. Successful treatment has been reported with corticosteroid (prednisone <= 30 mg/day) or anticoagulation with low-dose aspirin or heparin. Current data suggest that daily heparin given subcutaneously with or without one baby aspirin throughout the 2nd and 3rd trimesters is the most successful prophylactic measure. Recognition of the high-risk pregnancy should provoke intense perinatal scrutiny, which often leads to elective cesarean section.

Perhaps the greatest change in the management of SLE during the past two decades has been the realization that, for most patients, the disease can be controlled without large, prolonged doses of corticosteroids with their likely long-term complications.